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Teaching Enzyme Catalysis Using Interactive Molecular Dynamics in Virtual Reality

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Supporting Information

ABSTRACT: The reemergence of virtual reality (VR) in the past few years has led to affordable, high-quality commodity hardware that can offer new ways to teach, communicate, and engage with complex concepts. In a higher-education context, these immersive technologies make it possible to teach complex molecular topics in a way that may aid or even supersede traditional approaches such as molecular models, textbook images, and traditional screen-based computational environments. In this work we describe a study involving 22 third-year UK undergraduate chemistry students who undertook a traditional computational chemistry class complemented by an additional component which we designed to utilize real-time interactive molecular dynamics simulations in VR (iMD-VR). Exploiting the flexibility of an open-source iMD-VR framework which we recently described, the students were given three short tasks to complete in iMD-VR: (1) interactive rearrangement of the chorismate molecule to prephenate using forces obtained from density functional theory calculations; (2) unbinding of chorismate from the active site chorismate mutase enzyme using molecular mechanics forces calculated in real-time; and (3) docking of chorismate with chorismate mutase using real-time molecular mechanics forces. A student survey indicated that most students found the iMD-VR component more engaging than the traditional approach, and also that it improved their perceived educational outcomes and their interest in continuing on in the field of computational sciences.

KEYWORDS: Graduate Education/Research, Biochemistry, Computer-Based Learning, Computational Chemistry, Enzymes, Molecular Biology, Nanotechnology, Theoretical Chemistry, Undergraduate Research

INTRODUCTION

The teaching of chemistry inherently relies on models to represent the underlying molecular processes, structures, properties, interactions, behaviors, and physics which drives phenomenological chemical change. In a chemistry context, the importance of models derives from the fact that molecular changes are not often directly observable. In constructing a model, the choice of representation depends on the size and complexity of the chemical structure being examined; as complexity grows, it is increasingly important to have compact models for abstracting the structure to make it intelligible. Early in their chemical education, students are taught to use Lewis structures as molecular representations, which are shortly thereafter replaced by skeletal structures as the molecules become more complex. In typical first-year undergraduate classes, students are introduced to new representations, such as Newman projections, which are designed to capture 3D information in 2D.¹ In the teaching of molecular symmetry, it is common to rely on physical 3D molecular model construction kits that allow certain symmetry operations to be performed and demonstrated in a way that intuitively engages 3D spatial reasoning. In structural biology, coarse representations called ribbon or cartoon diagrams (also called Richardson diagrams)² are used to help simplify the visualization of protein secondary structure.

All these representations are useful in certain contexts, but they share a common drawback insofar as they lack time resolution, and thus lack a connection to the continuous motion which characterizes molecules, obscuring the critical role of dynamics and entropy in understanding chemical thermodynamics. University-level chemistry tends to be taught using static, time-independent representations such as skeletal structures. When molecular dynamics is directly tackled, it is often described in the form of mathematical representations. For example, the partition function, which forms one of the key concepts in statistical mechanics and transition state theory, is an integral over all the different ways that a molecule can translate, rotate, and vibrate. Similarly, entropy is fundamentally connected to a molecule's flexibility. In our experience, dynamics and entropy are abstract concepts that students can find difficult to grasp; however, visualizing molecular dynamics can aid students understanding of chemical principles.^{3,4} Therefore, an approach which dynamically represents molecules within a fully three-dimensional interface has great potential as a learning tool, and the extent to which dynamical representations help learning outcomes compared to static two-dimensional images is a viable avenue of research.

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New technological paradigms have been adopted in recent years to move beyond a static representation approach to university-level chemical education,^{5–7} offering alternative ways for students to understand molecular science outside the wet lab. For example, computational chemistry can provide students with the ability to watch screen-based movies of molecular motion or build structures for subsequent postprocessing using specialist codes, as well as introduce them to the power of computational workflows for understanding molecular processes. However, few tools enable students to intuitively interact with the rigorous dynamics that governs molecular motion, particularly in a manner that engages with and ultimately aids education. In the past few years, research within psychology and neuroscience has shown that multisensory processing increases attention.⁸ Inspired by findings like these, our group has actively been developing immersive technologies for enabling multisensory perception of nanoscale dynamics, exploring perceptual channels beyond vision, including audio, touch, and proprioception. In this work, we illustrate the use of research-grade simulation tools to enable interactive molecular dynamics simulations in VR (iMD-VR), which can be used to create multiperson interactive dynamics environments to help students learn about molecular motion and dynamics. In utilizing state-of-the-art tools like those described herein, students not only increase their understanding of chemical structure and dynamics but also gain fluency in using sophisticated visualization tools, providing benefit in the form of transferable skills and computer literacy which is practically useful beyond their university education. As a research field, computational chemistry is increasingly essential, providing insight into molecular physics, structural biology, and materials science, and driving progress in areas such as drug design, catalysis, and biochemistry,^{9–12} where it routinely provides molecular-level insight into experimental results and enables the investigation of areas which are difficult to study using standard laboratory and analytic tools.¹³

Important challenges arise in teaching computational chemistry techniques and tools during undergraduate degree programs. Because of the complexity of the field, most courses allot little time to the teaching of these tools as well as the required computer literacy. Moreover, given the wide range of domains where computational tools can be applied, it is not often possible to give more than a cursory introduction to some of the tools and the physical insight that they can provide. For example, training in one area, such as classical molecular dynamics using a force field approach, does not necessarily provide students with the tools to tackle other computational chemistry areas, such as electronic structure calculations. The difficulty is compounded by the fact that many computational tools are legacy scientific codes and, therefore, offer a user experience which feels dated compared to the sorts of apps to which students are often accustomed. For example, problems arise from the fact that molecular dynamics packages often require students to deal with bespoke (and often dated) input formats and bash scripting for the first time. Many computational chemistry codes are not user-friendly, requiring specialist training for each code and its associated jargon. A majority of the most popular molecular dynamics simulation packages were designed prior to the availability of modern human–computer interaction technologies (CHARMM¹⁴ for example can trace its origins back to the time of FORTRAN punch cards). Over the past several

years, we have run computational chemistry classes teaching students how to use these powerful but highly specialized legacy tools, and we have often found that it can be difficult to convince students that learning to use such tools is preparing them to cope with the workflows of the future.^{15–17}

Most common molecular viewer interfaces used for teaching chemistry require the user to interact with molecules through a traditional 2D interface. For complex 3D structures, such interfaces have clear limitations. The more popular molecular visualizers of the past 30 years provide a 2D perspective on what are naturally 3D structures and processes and also suffer colocation issues.¹⁸ The recent paper by O'Connor et al. described the colocation problem in detail.¹⁹ Briefly, perfect colocation arises when the interaction site in physical space is perfectly aligned with the interaction site in digital virtual space. For example, touchscreens achieve perfect colocation in 2D because the interaction site in physical space is identical to the interaction site in virtual space. This is a significant reason why children at a very young age find it straightforward to navigate a touchscreen. Programs such as Gaussview²⁰ or VMD²¹ which are primarily built to utilize a mouse and screen interface do not represent colocated forms of interaction. For understanding and manipulating complex 3D structures, the constraints of this type of interaction can lead to unintended motions (e.g., moving an atom out of a molecular axis by accident) and can be frustrating for students.

The work presented here describes an intuitive new set of computational research tools designed to solve the problem of 3D colocation, which can be utilized in traditional higher-education laboratory modules, in order to train students in computational approaches to molecular science, and also as a complement to understanding the fundamentals responsible for observations made during wet-lab work. We show how our open-source iMD-VR framework can be used to aid in teaching about molecular interactions, molecular forces, enzymology,²² mechanism generation, and protein–ligand docking. We show that students have a favorable response to this technology,^{17,23} which enables them to learn about dynamical aspects of molecular behavior they often find difficult to understand. The iMD-VR software we use for the real-time dynamical interactivity, NarupaXR,²⁴ is a state-of-the-art open-source project which enables multiple participants to cohabit the same iMD-VR environment to “reach out and touch” real-time research-quality molecular dynamics simulations, “feeling” their dynamical responses and manipulating their motion in real-time. The source code is available at ref 24 along with a stable beta executable at ref 25. Narupa builds on the capabilities of the proof-of-principle framework outlined by O'Connor et al.¹⁹ Narupa's flexible force API enables it to be set up for simulations using either quantum chemistry or molecular mechanics. Narupa can also be set up to run on local networks, ensuring good performance and low network latency for multiperson setups. In building Narupa, we have actively engaged with designers, artists, and human–computer interaction (HCI) experts, in order to create a framework which not only has scientific utility but also represents best HCI practice and is aesthetically compelling.

At present, there are a wide array of relatively distinct technologies which are often referred to as “virtual reality”. These can be distinguished according to the level of immersion which they offer. VR pioneers such as Jaron Lanier have emphasized this point, highlighting the fact that a number of frameworks which are often referred to as “virtual reality”

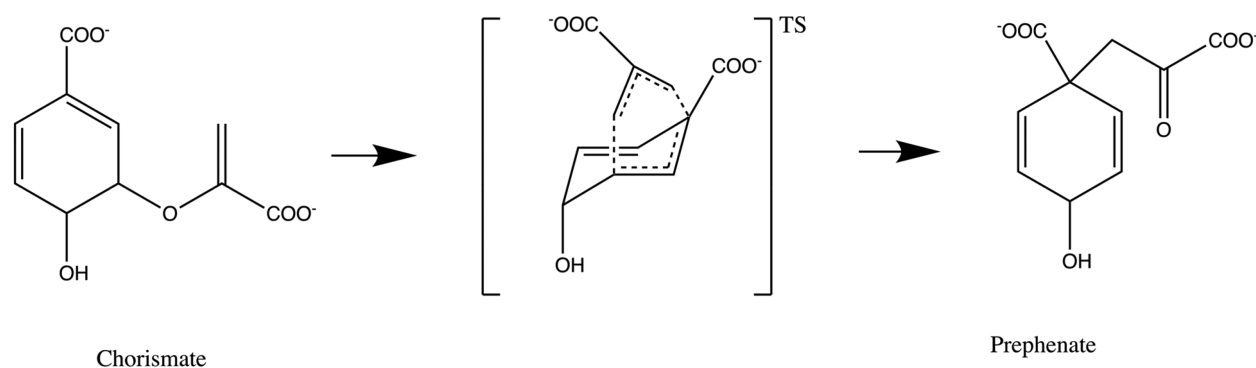


Figure 1. Reaction scheme for the rearrangement of chorismate into prephenate.

enable participants to do little more than “just looking around in a spherical video”.²⁶ Lanier, along with other HCI researchers, has made a point to distinguish those technologies which do afford reaching out to touch the virtual world: “If you cannot reach out and touch the virtual world and do something to it, you are a second class citizen within it... a subordinate ghost that cannot even haunt.” Mel Slater highlights a useful way to schematize different VR technologies according to the level of immersion which they offer.¹⁵ Any VR technology’s level of immersion can be defined relative to another VR technology by making a determination as to whether its affordances enable it to simulate in principle (or not) the experiences enabled by alternative VR technology. So we can say that a specific VR technology A is “more immersive” than another VR technology B so long as A could be designed (in principle) to simulate the experience of using B.

Our efforts to date have focused primarily on the HTC Vive, whose design affordances enable one to “reach out and touch” simulated realities like molecules. According to Slater’s definition, the HTC Vive (which utilizes sensors on the headset and controllers to allow real-time motion tracking) is among the most immersive of the commodity frameworks, in the sense that it could be designed to simulate the vast majority of other VR technologies (e.g., a CAVE, a Samsung Gear a Playstation headset, etc.), but not *vice versa*. Our software implementation permits multiple individuals to simultaneously cohabit the same simulated virtual reality space, enabling collaborative classes to be run using a room-scale setup in which students can walk around, interacting with one another and with simulated molecular objects in the virtual world, all of which is perfectly colocated in 3D. We believe that this immersive framework, which enables molecular interaction with atomically resolved precision, will prove more effective for teaching complex concepts, in particular, by providing higher engagement and a better perception of educational outcomes.

Enzyme Case Study

Over the past 8 years, we have run a class for third-year chemistry majors at the University of Bristol, which uses the CHARMM¹⁴ molecular simulation package to teach students about the rearrangement of chorismate to prephenate, first in vacuum, and then catalyzed by chorismate mutase. Chorismate mutase is a biosynthetic enzyme that is part of the pathway that results in the production of tyrosine²⁷ and is found in various nonanimal species. The chemical mechanism of the reaction is a Claisen rearrangement, illustrated in Figure 1, and involves distinct conformational changes in the ring as the reaction progresses from reactant to transition state, and then to product. Progress along the reaction coordinate is

straightforward to track visually by inspecting the cleavage of the ether bond as well as changes in the ring conformation. Transition state stabilization is an important factor in catalysis in this enzyme, and the stabilization provided by the enzyme along the reaction coordinate can be calculated using standard quantum mechanical/molecular mechanical (QM/MM) techniques.^{13,28–34} By comparing their work to the results of their peers, the students are able to relate the degree of stabilization to differences in the conformation of the enzymes and understand the relevance of transition state stabilization to catalysis.

Design of the Class

Our hypothesis when designing this experiment was that iMD-VR would enable better perceived learning outcomes and a better experience of computational molecular modeling and simulation techniques in chemistry. Our experience over the past several years has shown that a number of students found the standard CHARMM/VMD class frustrating due to a lack of familiarity with its text-based input syntax. We integrated iMD-VR into the aforementioned third-year undergraduate computational chemistry class, which is conducted over 2 days. The intended learning outcomes for this class are that the students should understand (1) the importance of protein–transition state stabilization for biomolecular catalysis, (2) how to calculate the stabilization energy provided by the enzyme, and (3) how to demonstrate how enzyme conformational changes affect reactivity. The class also aims to teach the students the difference between quantum mechanical (QM) and molecular mechanical (MM) calculations and how these methods can be combined to make up a powerful method called QM/MM (recognized in the 2013 Nobel Prize).^{35,36} The wider skills which we intend the students to learn during this class include an understanding of (1) the command prompt (bash), (2) the CHARMM molecular dynamics program and its input syntax, and (3) the use of the visualization program VMD.^{21,37} Through introducing iMD-VR, we aimed to compare a new teaching technology against the traditional CHARMM/VMD technology utilized in the class, as a process to study reactive conformations of chorismate and chorismate mutase, and also as a tool for the visualization of results.

The CHARMM/VMD section of the lab is based on lab teaching sessions run in previous years at The University of Bristol, where each student has a PC and uses CHARMM to model the enzyme catalyzed reaction of chorismate to prephenate and VMD to visualize the output (both programs were locally installed on the cluster computers). A more detailed description of the lab content can be found in ref 38,

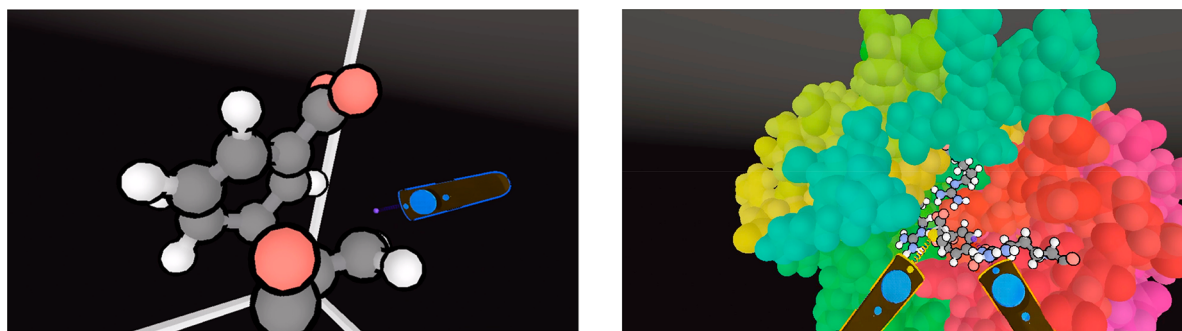


Figure 2. Left: A student's first-person view from within Narupa's iMD-VR environment as they interact with the α carbon with respect to the ring carboxylate of chorismate to perform the Claisen rearrangement. Right: A student reaching into chorismate mutase with two controllers.

such that the lab can be recreated, either with CHARMM/VMD or other similar software. Several demonstrators, who were versed in using the software and theoretical background of the lab, were also available to answer questions and deal with technical issues as they arose. We ran the iMD-VR component in a separate room, in an attempt to ensure that each student's iMD-VR starting point was similar. The students were taken to the iMD-VR room individually and introduced to the controllers. We described to students how the buttons on the real-world controls corresponded to actions in the iMD-VR simulation. For this study the students only needed to operate each controller's "trigger", enabling them to exert a force on a targeted atom, and manipulate its dynamics and motion. Each student was then provided a brief overview of the series of chemical tasks that they would be conducting and were given up to 10 min in iMD-VR to accomplish these tasks. Each student was offered an opt-out and nausea warning before they attempted the iMD-VR section, although zero students opted out and zero reported any discomfort. The three tasks which we instructed the students to undertake are shown in the supporting video available at ref 39 and included the following:

- (1) Claisen rearrangement of chorismate to prephenate via a cyclic transition state, as shown in Figure 1 and part A of the supporting video.³⁹ The reaction was conducted in a vacuum using real-time forces obtained from a semi-empirical quantum mechanical method called density functional theory tight binding (DFTB).⁴⁰ This technique was chosen because it is one of the fastest quantum chemistry methods available and, so, allows students to undertake real-time interaction with the molecules and model chemical reactions.
- (2) Removing the chorismate substrate from a setup in which the chorismate was bound to chorismate mutase, as shown in part B of the supporting video. In undertaking this unbinding procedure, students were instructed to minimize perturbation to the enzyme's structure by exercising precision and care, so as not to destroy protein secondary structure in the vicinity of the active site. For this purpose, three arginine side chains important for the binding of chorismate were highlighted in the representation (see the right of Figure 2). This allowed us to highlight to the students those residues where particular care was required.
- (3) With chorismate initially unbound to chorismate mutase, docking chorismate into the chorismate mutase active site so that it remained in a bound pose. An example is shown in part C of the supporting video.³⁹

Again, part of the challenge here is to utilize sufficient care and precision so as to not disrupt the secondary structure of the protein by not introducing too much energy into the chorismate molecule along its docking trajectory.

After all the students had completed the iMD-VR component and the CHARMM component, they were required to fill out a 22-question digital questionnaire about their experiences which was integrated into an online form hosted on the Bristol School of Chemistry Digital Laboratory Manual (DLM).⁴¹ The 22 questions were designed to gauge the student sentiment regarding the more traditional CHARMM/VMD approach compared to the iMD-VR component, and also to assess their prior experience with gaming, VR, and CHARMM/VMD. Of the questions asked, 20 gathered responses using a Likert scale and the final 2 collected long-form feedback. A detailed workflow for replicating this lab can be found in the Supporting Information (SI).

Simulation Setup

The simulations experienced (and driven) by the students used the following computational and physical conditions: Task 1 was run with a temperature of 300 K and a time step of 0.25 fs. The MIO parameter set⁴² was used in combination with a version of the DFTB+ code⁴⁰ that was modified to act as a library callable from within NarupaXR, taking advantage of its flexible API. Tasks 2 and 3 used a temperature of 300 K, a time step of 0.50 fs, and the amber ff99SB force field.⁴³ A Berendsen thermostat⁴⁴ was used throughout to maintain the target temperature. The graphical representation of the enzymes was chosen to remove some of the complexity from the secondary structure by using a space-filling van der Waals representation for the backbone of the enzyme, with only the chorismate and three arginine residues shown in an all-atom representation, as shown in Figure 2 and parts B and C of the supplementary video.³⁹ Detailed installation instructions for NarupaXR which include example enzymatic systems can be found at ref 25.

RESULTS AND DISCUSSION

The survey results collected from the students are presented below and in a raw data form in the Supporting Information. We have selected the most significant results to display graphically and discuss these within the main body of the text.

Prior Experience

We specifically set out to assess whether the prior experience of students in iMD-VR and computational chemistry correlated with their preference for either platform. The participants reported not having any familiarity with VR, on a scale of none

Table 1. Comparative Median Values and Interquartile Ranges That Show the 25% and 75% Quartile Ranges^a

Question	Statement for Response	CHARMM/VMD Platform		iMD-VR Platform	
		Median ^b (N = 22)	Interquartile Range	Median ^b (N = 22)	Interquartile Range
1	I enjoyed using [Platform]	2.0	1.00–3.00	5	4.00–5.00
2	I found [Platform] simple to use	2.0	1.00–3.00	4	4.00–4.25
3	[Platform] improved my understanding of molecular structure and movement	3.5	3.00–4.00	5	4.00–5.00
4	[Platform] helped me understand the difference between quantum mechanical and molecular mechanical calculations	2.0	1.00–3.00	4	3.00–4.25
5	When answering the marked lab quiz [Platform] played a dominant role in my visual recall of the enzyme	3.0	2.00–4.00	3	3.00–4.00
6	Visualizing chorismate/chorismate mutase in [Platform] aided my understanding of the reaction	3.5	2.00–4.00	4	4.00–5.00
7	Working with [Platform] has increased my interest in working with the computational sciences	2.0	1.75–3.25	4	3.00–4.25

^aThis data is further represented in Figure 3. ^bThe scale for response ranges from 1 to 5, with 1 indicating “disagree”, and 5 “agree”.

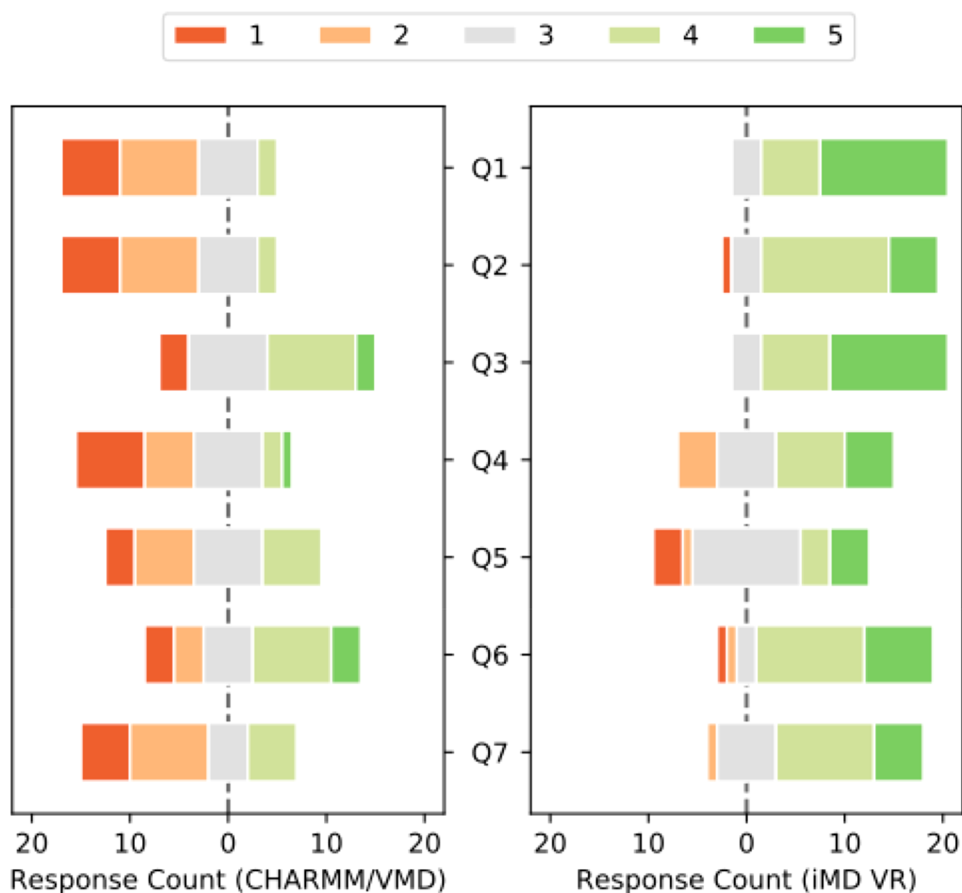


Figure 3. Divergent bar plot showing a comparison of student attitudes toward the CHARMM/VMD and VR platforms. Responses are given on a 5 point Likert scale, where 1 represents strong disagreement and 5 represents strong agreement. Plots that are skewed to the right (and green) are answers in agreement to the question, whereas questions skewed to the left (and red) of three indicate disagreement. The left-hand plot shows the results for CHARMM/VMD and the right-hand plot shows the results for VR.

(1) to extensive (5). The median value obtained was 1, with an interquartile range of 1–2. Their reported familiarity with computational chemistry was higher, with a median value of 2.5 and an interquartile range of 2–3. The survey asked the participants if they agreed with the statement “I play video games in my spare time”. This question aimed to gauge their overall familiarity with computer games which may prime their expectation on how to interact with 3D systems and prepare them for the non-mouse-based interaction. On a scale of disagree (1) to agree (5), the students reported a median of 3

and an interquartile range of 2–4. This distinctly average result suggests a relatively even spread of experience with gaming.

Platform Comparison

The student sentiment from the survey comparing CHARMM/VMD to iMD-VR has been collated in Table 1, with corresponding statistics for each of the 14 platform comparisons. The questions posed in this section ask a student if a given platform was enjoyable or simple to use and other qualitative questions; a response of 5 on the scale indicates a positive response in agreement with the question. These

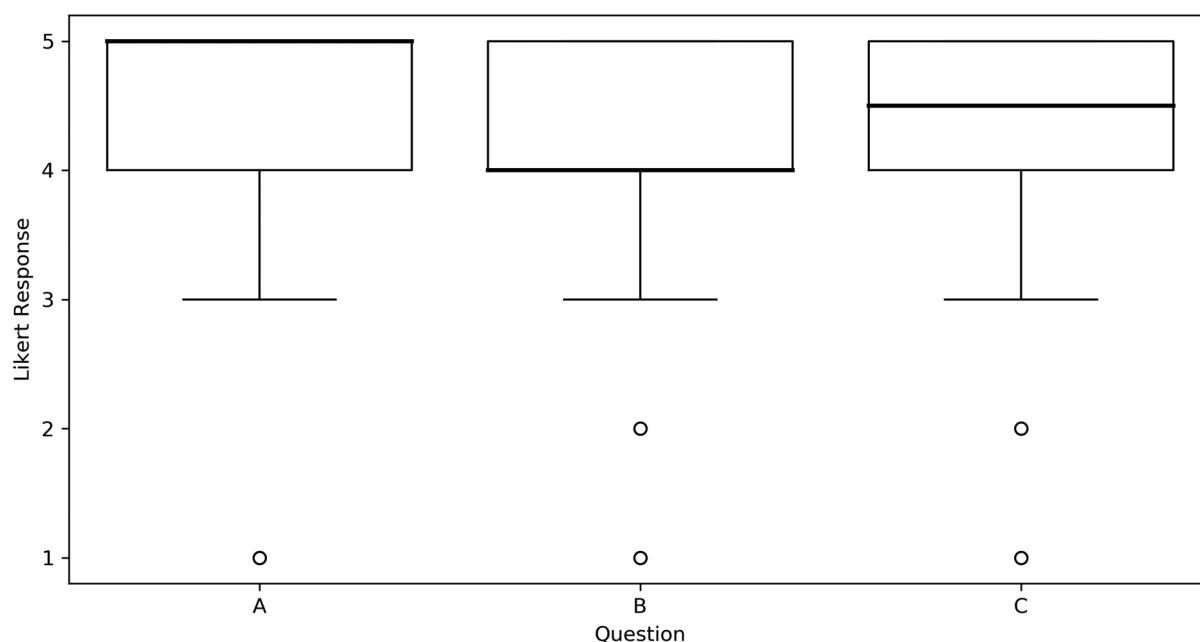


Figure 4. Responses of students to questions relating to their ability to perform biomolecular manipulation tasks in VR, given on a 5 point Likert scale, where 1 represents strong disagreement and 5 represents strong agreement. The questions were as follows: (A) I was able to bind chorismate into chorismate mutase in VR; (B) I was able to recognize the orientation of chorismate in chorismate mutase in VR; (C) I was able to rearrange the chorismate molecule in VR.

questions were asked using a Likert scale between disagree (1) and agree (5). This table presents both the median values and the interquartile values showing where the lowest 25% and highest 75% responses fall as a measure of answer skew. Figure 3 shows a visualization of the response data, utilizing a divergent stack plot centered on answer 3 (between agree and disagree) to help illustrate the differences between iMD-VR and the CHARMM/VMD class. We have also color coded the answers where a value of 1 (disagree) is in red and a value of 5 (agreement) is green. A red bar with a skew to the left of Figure 3 indicates that the question resulted in disagreement by the participants, and a green bar with a skew to the right is indicative of agreement. Inspection of Figure 3 shows that students answered more agreeably (and positively) for iMD-VR than they did for CHARMM/VMD.

The question that resulted in the most similar distribution for the two platforms was question 5, which asked if a platform played a dominant role in the student's visual recall. Table 1 shows that for this question the median value for both platforms is 3; however, the interquartile ranges indicate that iMD-VR had fewer disagreement responses (range 3–5 compared to 2–5 for CHARMM/VMD). In interpreting the responses to this question, an important factor to bear in mind is that the students only had 10 min in iMD-VR whereas they had 12 h to work with CHARMM/VMD. This provides some indication of how powerful even a small amount of time in iMD-VR can be for influencing visual recall. Questions one and two asked students if they found the platforms enjoyable and easy to use, and Figure 3 shows that participants agreed that the iMD-VR was easy to use, whereas they found CHARMM/VMD generally harder to use. For these questions, iMD-VR showed agreement responses with median values of 4 and 5 while CHARMM/VMD resulted in values of 2. These responses indicate that iMD-VR was more appealing for students to work with compared to CHARMM/VMD and suggests that iMD-VR is a tool that may improve student

engagement. Question 7 also indicates that iMD-VR may attract students to the computational sciences, with Figure 3 showing many more responses indicating agreement with the question for iMD-VR, with the median of these responses being 4, whereas CHARMM/VMD had a median of only 2. In combination with the earlier two questions measuring enjoyment and degree of simplicity, there seems to be a strong indication that the students have a positive perception of iMD-VR. The Figure 3 results highlight the potential for state-of-the-art immersive tools like iMD-VR to have a profound effect on the student outlook in computational fields.

The participants indicated that iMD-VR was better at helping them understand molecular structure and movement (Q3) with a median value of 5 and an interquartile range of 4–5 compared to CHARMM/VMD, which had a median of 3.5 with a range of 3–4, despite only having a short time in iMD-VR (although the novelty effect cannot be discounted without further research). The immersion in a dynamic simulation, in this case, appears to have a clear effect on the students' perspective on the nature of molecular motion. An unexpected result was that iMD-VR seemed to help students feel they better understand the difference between QM and MM calculations compared to CHARMM/VMD. When asked about the utility of iMD-VR and CHARMM/VMD for helping participants understand the difference between QM and MM calculations, the median value was 4 for iMD-VR and only 2 for CHARMM/VMD. This was surprising because the CHARMM/VMD section of the class explicitly demonstrated how students can set up QM/MM calculations. The response to this question may indicate that, despite understanding the terminology, the experiential difference (i.e., being able to interactively break and make bonds in iMD-VR) enhances their understanding. When asked if a platform aided the understanding of the reaction in Q6, the survey indicated that the participants found iMD-VR to help their visualization more than CHARMM/VMD. iMD-VR obtained a median value of 4

whereas CHARMM/VMD has a median of 3.5. Despite the similarity of these values, there is a marked difference in their interquartile spreads. CHARMM/VMD has values between 2 and 4, and iMD-VR has values between 4 and 5, indicating more consistency for the iMD-VR responses compared to the CHARMM/VMD responses.

iMD-VR Task Completion

The rate of scientific task completion is as important as student preference in showing that iMD-VR is a viable tool in university-level chemistry education. Figure 4 shows students' reports on their ability to complete each of three iMD-VR tasks. All three tasks showed medians above 4, and 25% quartile ranges above 3.5 indicating high rates of task completion. In particular, the participants reported being able to dock/bind chorismate into the highlighted active site (left-most panel) with a median value of 5 and a lower quartile value of 4 indicating that the students believe they completed this molecular binding objective. This task is of particular interest in domains such as structure-based drug design, for which discovering docking poses is an important way to find new drug leads. The ability of students without prior experience in either docking or iMD-VR to perform this task quickly shows the power that iMD-VR tools may have in accelerating traditional drug binding studies. These results suggest that students could perform such actions early on in their studies and improve their understanding of pharmacological problems. Data from such classes could potentially be collected and studied with the aim of generating ensemble starting points for high-quality statistical data to analyze binding energies, mechanisms, and poses. Column C in Figure 4 refers to the quantum rearrangement of chorismate to prephenate; the results show that the students felt that they were able to manipulate the chemical system. Anecdotally, we observed during these simulations that students struggled to recognize the functional groups of chorismate, despite having been furnished with structure diagrams as shown in Figure 1. This may indicate that their familiarity with 2D projected structural diagrams does not transfer into an ability to recognize 3D chemical structures and more broadly suggests that 2D training in molecular visualization is not immediately transferable to 3D spatial reasoning, potentially affecting the way that students approach chemical problems. This is a point which we intend to study in further detail in future work.⁴⁵

Student Lab Marks

This lab did not attempt to quantify the direct learning gains of the participants; however, we note that students that experienced iMD-VR obtained a median score of 80/100 overall for this lab, whereas students who took part in the lab before the VR component was added scored a median value of 65/100. These results do not conclusively prove that there were educational gains from experiencing iMD-VR but may indicate that there are improvements in learning. A full study to assess these effects will need to be run in order to properly assess educational gains.

Long-Form Answers

The participants were also asked to give long-form answers on their impressions on both platforms (full responses are given into the SI). For iMD-VR, the comments were nearly entirely positive with comments such as "interesting", "good fun", and "great experience". For CHARMM/VMD, the sentiment was less enthusiastic, with comments such as "lots of fiddling",

"infuriating", and "a touch confusing". As an approximate measure of sentiment, we utilized Microsoft Azure cognitive analysis^{46,47} on the collected text answers obtained for both platforms. This model uses a machine learning approach to analyze text-based input and detect sentiment, scaling it between a value of 100% for positive and 0% as negative. iMD-VR resulted in a value of 100% and CHARMM/VMD as 2%. Google cloud⁴⁸ offers a similar set of tools and gauges sentiment between -1 (negative) and +1 (positive). Using these tools, the CHARMM/VMD exercise scored as -0.3, whereas iMD-VR obtained a score of 0.9. Neither of these models are exact measures of sentiment; however, they are broadly indicative that the sentiment for iMD-VR is much more positive than for CHARMM/VMD.

CONCLUSIONS

To date, there are few studies examining the use of iMD-VR as a chemistry teaching tool in higher education. Its effects on both student sentiment toward computational science and its ability to support learning objectives are worth further investigation. The work we have presented here shows that iMD-VR is an effective and practical tool for demonstrating biochemical processes to undergraduate students. Primarily, this work shows not only that iMD-VR improves students' impression of computational molecular science and their overall sentiment toward molecular simulations, but that it also has a positive effect on their own perceived learning outcomes. Our decision to carry out studies aimed at assessing the extent to which university students perceive iMD-VR to positively impact their educational experience is a result of the fact that UK universities are currently implementing a new national framework for assessing teaching called The Teaching Excellence and Student Outcomes Framework (TEF). TEF places significant emphasis on "student satisfaction", which it measures through national student surveys aimed at characterizing how students perceive their university learning experience.

Given this emerging emphasis in UK education, we believe that the results outlined herein, demonstrating that iMD-VR enhances the student experience, are a necessary prerequisite prior to further studies, in which we will measure the impact our iMD-VR framework has on learning outcomes. Nonetheless, with the changing landscape of undergraduate education, it is important that chemistry courses keep up with state-of-the-art technological developments and enable students to become comfortable with emerging simulation and visualization approaches that are becoming increasingly ubiquitous across several fields beyond chemistry.¹⁵ The results discussed herein indicate that iMD-VR has the potential to form an important part of this process. Narupa enables students to interact with molecular motion, and chemical reactions, in an immersive environment that not only enhances learning but also allows students to perform complex molecular operations such as docking of substrate or inhibitor molecules into enzymes, and driving conformational and chemical changes. Clearly, iMD-VR has the potential to contribute to education in all disciplines that involve the study of molecular or solid structures, e.g., materials science, structural biology, biochemistry, and related disciplines. iMD-VR could have profound effects on changing what is achievable within undergraduate courses. In future work we plan to explore the extent to which training students with 2D models transfers to 3D intuition and also evaluate the effects of group iMD-VR work compared to

individual work. In particular, we will carry out studies designed to enable an instructor to cohabit the iMD-VR environment alongside students, in order to guide them through various computational chemistry/molecular modeling tasks, demonstrate principles and, e.g., reaction mechanisms, and quantify the educational benefit of this approach. We hope that in these studies it will be possible to understand if VR and the choice of chemical representation can have a positive impact on recruiting more diverse sets of computational chemists.

■ ASSOCIATED CONTENT

● Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: [10.1021/acs.jchemed.9b00181](https://doi.org/10.1021/acs.jchemed.9b00181).

Lab procedure for the study of the binding/unbinding of chorismate with chorismate mutase and the rearrangement of chorismate mutase to prephenate (PDF, DOCX)

Questions asked in the survey and the responses collected from students (PDF, DOCX)

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Notes

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